heavy chains; antibody heavy chains or fragments thereof, optionally associated with the respective light chains; antibody Fab domains;] and IL-6, IFN-β, thrombopoietin (TPO) or fragments thereof.

Claim 6, line 7, delete "dimer complex" and insert therefor --heterodimer--.

Please cancel claim 14 without prejudice and add new claim 21 as follows:

--15. The hybrid protein of claim 1, wherein each of said two coexpressed amino acid sequences forming a heterodimer consists essentially of sequences (a) and (b).--

REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claims are allowed. Claims 1-13, 19, and 21 presently appear in this application (with claims 7-13 remaining withdrawn) and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-6, 14 and 19 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendments to claims 1 and 2 and by the cancellation without prejudice of claim 14.

Claims 1-5, 14 and 19 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The examiner states that enablement is not commensurate in scope with claims wherein portion (a) is an antibody or other protein that is in and of itself dimeric in nature. As stated in the above rejection under 35 U.S.C. §112, second paragraph, and using an antibody as an exemplary species, the examiner holds that such an antibody would already be a dimer. It is noted by the examiner that claim 1 includes the limitation that the protein dimerize by aggregation of portions (b) of the fusion protein. The examiner asserts that the specification has not taught how to promote dimerization preferentially through portion (b) of the molecule in those species wherein portion (a) is additionally capable of dimerization. In those instances in which either end of the recited protein is capable of dimerization, the examiner takes the position that it is not predictable which end would predominate, nor how to control such and that it would seem that such would be dependent upon the respective kinetic of the two possible dimerization events, and that in some instances, both might be able to occur. Given the unpredictability and lack of guidance, the examiner concludes that it would require undue experimentation to determine how to assure that dimerization would occur via the (b) moiety. This rejection is respectfully traversed.

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Claim 2 is now amended to delete recitation of antibody chains or fragments and therefore sequence (a), recited in Markush format, does not encompass a protein that is in and of itself dimeric in nature. With regard to the remaining rejected claims, applicants submit that for two sequences (a) which form a dimer in nature it does not matter what are the respective kinetics of the two possible dimerization events. If dimerization first occurs through sequences (a), then subsequent dimerization of sequences (b) will provide the natural heterodimeric scaftolding corresponding to a circulating non-immunoglobulin protein with a long half-life that is the purpose of the present invention (see the present specification, page 4). The dimerization of sequences (b) to form a heterodimer and to stabilize the dimer of sequences (a), when such sequences are dimeric in nature, is one object of the present invention. Therefore, for sequences (a) that are dimeric in nature, it is intended that the heterodimer formed by sequences (b) provide added stability. As disclosed in the specification, sequences (a) and (b) can be linked by a peptide linker which can act as a tether or flexible hinge region. This would allow both dimerization events to occur without conformational constraints. If sequences (a) dimerize first, this would only serve to place sequences (b) in closer proximity to each other and favor a second dimerization, and vice versa. Accordingly, the presently claimed is well-enabled to those of skill in the art.

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Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-5, 14 and 19 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Boime, U.S. Patent 5,705,478, for the reasons cited in the Office Action of May 22, 1998, at pages 4-5. The examiner indicates that while applicants' arguments addressed point (B) raised by the examiner, points (A) and (C) remain valid and the rejection is maintained on those bases. This rejection is respectfully traversed.

With respect of point (A), it is true that while proteins are not rigid in their naturally-occurring forms, this does not hold where the protein (as a suitable drug) is used within a linker moiety between two gonadotropin subunits as taught by Boime. One of ordinary skill in the art cannot make any prediction about conformation of the protein because it has lost at two degrees of freedom by being linked to another molecule both at its head and tail. Therefore, it is more rigid than the corresponding naturally occurring form.

More importantly, Boime is directed to single chain proteins. Even if Boime's single chain proteins can form dimers or multimers with itself, these multimers would still be the product of a single chain protein with a single amino acid sequence. By contrast, claim 1 is now amended to recite that it is two <u>different</u> coexpressed amino acid sequences that form a heterodimer. There is no disclosure or teaching in Boime to make

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